Effects of Noninvasive Ventilation on Sleep Outcomes in Amyotrophic Lateral Sclerosis

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Study Objectives: The objective was to study the effects on noninvasive ventilation on sleep outcomes in patient with ALS, specifically oxygenation and overall sleep quality.

Methods: Patients with ALS who met criteria for initiation of NIV were studied with a series of 2 home PSG studies, one without NIV and a follow-up study while using NIV. Primary outcome was a change in the maximum overnight oxygen saturation; secondary outcomes included change in mean overnight oxygen saturation, apnea and hypopnea indexes, sleep latency, sleep efficiency, sleep arousals, and sleep architecture.

Results: A total of 94 patients with ALS were screened for eligibility; 15 were enrolled; and 12 completed study procedures. Maximum overnight oxygen saturation improved by 7.0% ($p = 0.01$) and by 6.7% during REM sleep ($p = 0.02$) with NIV. Time spent below 90% oxygen saturation was also significantly better with NIV (30% vs 19%, $p < 0.01$), and there was trend

for improvement in mean overnight saturation (1.5%, $p = 0.06$). Apnea index (3.7 to 0.7), hypopnea index (6.2 to 5.7), and apnea hypopnea index (9.8 to 6.3) did not significantly improve after introducing NIV. NIV had no effect on sleep efficiency (mean change 10%), arousal index (7 to 12), or sleep stage distribution (Friedman chi-squared = 0.40).

Conclusions: NIV improved oxygenation but showed no significant effects on sleep efficiency, sleep arousals, restful sleep, or sleep architecture. The net impact of these changes for patients deserves further study in a larger group of ALS patients.

Keywords: ALS, bilevel PAP, noninvasive ventilation, sleep, motor neuron disease

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Sleep dysfunction is commonly seen in patients with amyotrophic lateral sclerosis (ALS) through a number of nonrespiratory (psychological stress, pain, cramps) and respiratory (sleep apnea, hypoventilation) mechanisms.¹ Most sleep dysfunction occurs later in the course of the illness, particularly when diaphragmatic dysfunction occurs and respiratory compromise becomes evident.² The mechanisms underlying respiratory dysfunction during sleep in ALS depend on multiple factors, including the disease stage and whether or not the diaphragm is involved.

The most effective interventions for respiratory and sleep dysfunction in ALS include noninvasive ventilation (NIV), which has been shown to improve respiratory parameters, survival and quality of life.³⁻⁶ The 2009 American Academy of Neurology Practice Parameter on ALS treatment recommended the use of NIV for patients demonstrating evidence of respiratory compromise.⁷ A recent Cochrane Review also evaluated the effects of night-time mechanical ventilation in patients with neuromuscular or chest wall disorders, including patients with ALS.⁸ The review concluded that there was a mild but consistent effect of nighttime mechanical ventilation on symptoms of chronic hypoventilation and survival and a lack of data on the effects on sleep outcomes in these disorders.

To date, there are no studies reported in which the primary aim is to specifically evaluate the effects of NIV on sleep outcomes. As NIV is already indicated for use in ALS patients experienc-

BRIEF SUMMARY

Current Knowledge/Study Rationale: Previous studies have evaluated the effects of non-invasive ventilation, namely BiPAP, on morbidity and mortality in patients with ALS. Details regarding the specific effects on sleep outcomes have not been previously studied in detail.

Study Impact: Knowledge of the specific effects of non-invasive ventilation on sleep parameters in ALS can help improve the way this technology is currently used in this unique patient population. It also provides information that can be used by developers to create more advanced patient-oriented ventilator systems.

ing respiratory dysfunction, the goal of this study is not to find a new indication for NIV in ALS, but rather to better understand its effects on sleep outcomes and sleep disordered breathing. The specific study aims are to evaluate the effects of NIV on oxygenation, overall sleep quality and other parameters such as apnea index, sleep latency, arousals, and total sleep time.

METHODS

Study Design

We performed a pilot, self-controlled study in patients with a confirmed diagnosis of ALS who were starting noninvasive ventilation (NIV) for impaired respiratory or sleep function.

Table 1—Inclusion and exclusion criteria

Inclusion Criteria:	Exclusion Criteria:
<ul style="list-style-type: none"> • Age 18 or older • Participants with familial or sporadic ALS diagnosed as laboratory-supported probable, probable, or definite according to the modified World Federation of Neurology El Escorial criteria will be eligible • Patient requires use of NIV because the patient: <ol style="list-style-type: none"> 1) has FVC < 50% 2) has MIP less than -50 cm H₂O 3) has symptoms of nocturnal hypoventilation and nocturnal arterial oxygen desaturation (SaO₂ < 88% for > 5 min or for > 10% of total monitoring time) 4) has development of daytime hypercapnia (PaCO₂ > 6.5 kPa) • Informed consent from patient or designated representative • Negative pregnancy test in females of child-bearing potential 	<ul style="list-style-type: none"> • Patient in on mechanical or artificial respiration • Underlying sleep or respiratory disorders present prior to ALS that would affect sleep outcomes independent of ALS. • Current pregnancy or breastfeeding • Significant decision making incapacity preventing informed consent by the subject due to a major mental disorder such as major depression or schizophrenia, or dementia such as having Alzheimer disease. • Inability or unwillingness to undergo home polysomnography

ALS, amyotrophic lateral sclerosis; FVC, forced vital capacity; MIP, maximum inspiratory pressure; NIV, noninvasive ventilation.

Patients were recruited from the Stanford Hospital ALS Clinic and Forbes Norris ALS Research Center from February 2009 to February 2010. The local ethics committees at both centers approved the study. All patients gave written informed consent in accordance with the Declaration of Helsinki.

Criteria for inclusion and exclusion are described in **Table 1**. Patients were screened by the evaluating neurologist (HDK) during their routine clinic visit to the ALS clinics, which occurs on average every 3 months. Once the patient was identified as a candidate for the study and provided consent, a baseline home polysomnogram (PSG) was performed without NIV within 4 weeks of the screening visit. A follow-up PSG was performed once the patient was comfortable with the complete (> 80%) overnight use of NIV throughout the night. Changes in sleep outcomes before and after NIV are reported.

Clinical Measures

At the initial screening visit, each potential study candidate had full neurological assessment by a neurologist, including measurement of a 48-point ALS Functional Research Score (ALSFR-S).⁹ Forced vital capacity (FVC) and mean inspiratory pressure (MIP) measurements were also performed at the screening visit by the clinic respiratory therapist (LG) or at the hospital spirometry laboratory. Vital capacity was measured with a Renaissance spirometer (Puritan Bennett, USA). Maximum inspiratory pressure (MIP) was measured with a handheld meter (Precision Medical, Pickering, UK). An adapted anaesthetic mask was used to overcome the problem of mouth leak in people with bulbar or facial muscle weakness. Measurements of vital capacity were expressed as percentage of predicted. MIP was measured as negative pressure in centimeters of water pressure (cm H₂O). During the screening visit, the evaluating neurologist (HDK) performed a sleep history on each potential patient, including an Epworth Sleepiness Scale (ESS). The ESS quantifies daytime sleepiness with a maximum score of 24; most patients without documented sleep dysfunction have a score ≤ 10.¹⁰ At the end of the study, a post-intervention questionnaire was administered to determine if both the sleep study and NIV were well tolerated; the visual analogue scale ranged from 0 to 10, with 0 being not tolerated at all and 10 being no issues with the intervention.

Noninvasive Ventilation Settings

All patients used bilevel positive airway pressure, with average-volume assured pressure support ventilation at the time of the second sleep study. Home care respiratory therapists fit the patient with mask and alternatives, placed the patients on initial settings and titrated settings for patient comfort. Initial settings start in the low range (6-7 mL/kg ideal body weight for volume-targeted pressure support) to aid in acclimatization to the device. All patients were reassessed after initiation of NIV and prior to the second sleep study to ensure adequate mask fitting, volume, pressure, and rate targets in each patient. Adjustments were made as expeditiously as possible in order to avoid unnecessary titration delays which are sometimes experienced in the clinical setting and which would affect our study results due to progression of the disease. Settings at the time of the study ranged as follows: targeted volume (Vt) = 240-480 mL, maximum inspiratory positive airway pressure (IPAP) = 14-20, minimum IPAP = 6-8, expiratory positive airway pressure (EPAP) = 4-8, backup respiratory rate = 10-12. No supplemental oxygen was used in any of the 12 patients studied and none of the patients had major difficulties fighting the NIV or with mask tolerance.

Home Polysomnography Setup

Patients underwent home PSG using a Crystal 20b system (Clevemed Medical Devices Inc). The Crystal 20b PSG Series is a 14-channel type 2 monitor which includes 4 electroencephalogram (EEG) channels (occipital, central, and ear reference locations), 1 electrooculogram (EOG) channel, 1 airflow channel using a mouth thermistor or nostril pressure probe, 1 channel for chin and 1 for leg EMG movement, 1 channel for electrocardiogram (EKG), 1 channel for a pulse oximeter, 2 channels for measuring chest wall and abdominal movement, 1 channel for body position, and 1 channel for snoring detection. Home PSG set-up was performed by a registered sleep technologist (AS) or physician (HDK). Sleep recordings were analyzed using both an automatic software package and were double-checked by both a registered sleep technologist (AS) and physician sleep specialist (NY), both unaware of the whether the patient had NIV.

Sleep Outcome Measures

Oxygenation parameters measured included improvement in minimum overnight oxygen saturation, mean overnight

saturation, time spent below an oxygen saturation of 90%, and minimum oxygen saturation with NIV. Respiratory specific secondary outcome measures included changes in apnea index (AI), hypopnea index (HI), and apnea/hypopnea index (AHI). Other secondary sleep related outcome measures included changes in arousal index, total sleep time (TST), total sleep period (TSP), sleep efficiency, amount of time spent in each sleep stage (stages 1-3 and REM), and sleep latency. Sleep stages and other sleep parameters were scored according to the American Sleep Medicine Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specification.¹¹ Apneas were defined as a cessation of airflow ≥ 10 sec, and AI as the total number of apneas/h of sleep. Hypopneas were defined as $< 50\%$ of airflow for 10 sec, and the HI as the total number of hypopneas/h of sleep. AHI was defined as the total number of apneas and hypopneas/h of sleep. Arousal index was defined as the total number of arousals/h after the first stage of sleep is scored; arousals were defined as any change from a deeper to lighter stage of sleep or wakefulness. TST was defined as the total time spent in stages 1-3 or REM sleep, TSP as the time in bed from lights out to lights on, sleep efficiency as TST divided by TSP, and sleep latency as the amount of time it took for the patient to fall asleep after lights out. Amount of time spent in each sleep stage was reported as a percentage of time in that particular sleep stage divided by TST.

Statistical Analysis

This was a pilot study, and as such, its aim was not to detect significant differences in most of the relevant sleep related outcomes. A power calculation was nevertheless performed to estimate the number of patients needed to detect a significant change one of the oxygenation outcomes: minimum overnight oxygen saturation between the baseline and follow-up PSG. A change in oxygen saturation of 5% with a variance of 5% was used based on previous studies⁸ evaluating effects of NIV on overnight oximetry in patients with neuromuscular disorders, which showed an average of 3% to 5% improvement in mean overnight oxygenation. Using α of 0.05 and β of 0.8, an estimate of 12 patients (2 studies per patient, 24 studies total) was determined to be necessary to detect a change in minimum overnight oxygen saturation. Changes in the oxygenation and other sleep outcomes were compared between baseline and follow-up NIV sleep study using Student t-test. Friedman two-way analysis of variance by ranks was used to detect significant changes across the different sleep stages.

RESULTS

We screened a total of 94 consecutive patients with a diagnosis of ALS for inclusion into the study and recruited 15 patients about to start NIV. Seventy-nine patients were not included, because patients had end-stage disease requiring hospice (4 patients), were already on NIV (12 patients), or did not require NIV as respiratory function was above cutoffs for NIV recommendations (63 patients). Three patients who were enrolled in the study were not able to complete the follow-up sleep study: one patient due to inability to tolerate NIV, one patient who passed away prior to the second sleep study, and one patient

Figure 1—Flowchart of patient participation

due to reclassification to Creutzfeldt Jacob Disease with motor neuronopathy from the initial diagnosis of sporadic ALS (Figure 1).

Clinical and Sleep Characteristics at Screening

Table 2 summarizes the clinical and sleep characteristics at screening between the patients included in the study and those excluded from the study. There were no bulbar onset patients included in the study, compared with 15% in the excluded patients. Although the ALSFR-S total scores were similar in both groups, the patients included in the study had more advanced respiratory involvement, as evidenced by significantly lower ALSFR-S respiratory scores and FVC. The 12 patients included in the study showed a higher frequency of nighttime respiratory dysfunction at screening by history compared to the excluded patients: ESS, drop in FVC from supine to upright position, orthopnea, and observed apneas were significantly higher in the study patients. Only 1 patient in the enrolled patients had abdominal paradox compared to 5 in those not enrolled. None of the patients in the study had gastrostomies inserted at the time of the study compared to 9 patients in the patients not enrolled. Patients in both groups had comparably low BMI and neck circumference.

PSG Results: Oxygen Saturation

Figure 2 depicts changes in oxygen saturation between the NIV and the baseline sleep studies in our study. There was an improvement of 7% in minimum overnight oxygen saturation, the primary outcome, in ALS patients when using NIV ($86\% \pm 4\%$) compared to the baseline study ($79\% \pm 9\%$, $p = 0.01$; Figure 2). Ten patients had showed some improvement in minimum overnight oxygenation, and 3 patients improved more than 15% with NIV. Change in mean overnight oxygen saturation (94% vs 95.5% , $p = 0.06$) did not show a statistically or clinically meaningful change and proportion of sleep time spent $< 90\%$ oxygen saturation (30% vs 19% , $p < 0.01$) was significantly less when patients used NIV. There was a greater change in minimal oxygen saturation with NIV during REM (81.2% to 87.8% , $p = 0.012$) compared to other sleep stages (83.1% to 84.4% , $p = 0.46$). There was no relationship between age, sex, disease duration, sedative use, or FVC at time of study initia-

Table 2—Baseline clinical and sleep characteristics of all patients screened

	Patients included (n = 12)	Patients excluded (n = 79)
Age (years)	66 ± 17	47 ± 13
Females (%)	58	42
Bulbar onset (%)*	0	15
Duration of symptom (months)	19 ± 11	11 ± 6
Riluzole use (%)	71	52
Nighttime sedative use (%)	27	33
Gastrostomy	25	13
ALSFR Total Score (/48)	28 ± 10	32 ± 7
ALSFR Respiratory Score (/12)*	5 ± 2	9 ± 3
Gastrostomies (%)	8.3	11.4
Abdominal Paradox (%)	0	5.1
Mean change in FVC from supine to upright (%)	24 ± 8	17 ± 10
Neck circumference (cm)	33.0 ± 9	31.2 ± 9
BMI (kg/m ²)	21 ± 6	24 ± 10
FVC (upright) (%)*	53 ± 11	77 ± 15
Night cramps (%)	33	52
Night pain (%)	23	32
Excessive saliva at night (%)	13	18
Orthopnea (%)*	58	28
Observed hypopnea/apnea (%)*	50	30
Nighttime awakenings	4.1 ± 3.4	2.8 ± 1.2
Naps (min/week)	247 ± 100	220 ± 71
Epworth Score (max 24)*	14 ± 8	6.5 ± 4
Morning headaches (%)	38	28

*p < 0.05. ALSFR, amyotrophic lateral sclerosis functional rating; FVC, forced vital capacity; max, maximum; cm, centimeters; BMI, body mass index. Means ± standard deviations are presented for continuous variables and percentages for categorical variables.

tion and any of the predetermined oxygenation parameters, although power to detect such relations was limited.

PSG Results: Secondary Outcomes

Table 3 shows changes in all sleep parameters between the NIV and baseline PSG studies in each study patient, and **Table 4** shows the mean changes in the entire cohort. Sleep efficiency increased by 10% in the entire group of patients, which was not significant ($p = 0.15$); however, in a group of 8 of 12 patients, an improvement of almost 20% was seen. Respiratory parameters did not change significantly with NIV use: there was an improvement of 3 points ($p = 0.17$) in the apnea index and improvement in the hypopnea index of 0.5 points ($p = 0.72$), resulting in an improvement of 3.5 points in AHI ($p = 0.20$). Most of the apneas and hypopneas in our group were central (57%), with mixed apneas (26%) and obstructive apneas (17%) making up the remaining episodes. Evaluation of individual patient data reveals that most patients' respiratory parameters did not change much and in fact worsened in approximately half of the cases. The small mean improvements are largely due to 2 patients. In patient 3, apneas essentially all converted to hypopneas; while

Figure 2—Change in minimum overnight oxygen saturation between baseline and noninvasive ventilation (NIV) sleep studies in the 12 patients included with amyotrophic lateral sclerosis

this was one of the few patients with worse sleep efficiency, he also had one of the largest improvements in minimum overnight oxygen saturation. Patient 5 also had a large improvement in AHI, mediated by a cessation of essentially all hypopneas.

In our cohort, arousal index worsened nonsignificantly by 5 points with use of NIV ($p = 0.62$). Sleep quality did not improve with NIV; there was no change in percentage of restful sleep (stage 3, $p = 0.69$ or REM, $p = 0.40$) in response to NIV. Also, overall sleep architecture, reflected by a significant shift in any of the sleep stages, remained unchanged with NIV (Friedman $\chi^2 = 0.4$). There was no relationship between the time interval from the baseline sleep study to the second NIV sleep study (mean duration 9.0 ± 2.3 days) and any of the oxygenation or secondary sleep parameters.

Epworth scores did not change significantly after the first and second sleep study (14.8 to 12.4 , $p = 0.24$). Results of the post-study questionnaire showed that patients appeared to tolerate both the NIV (mean 8.1 ± 3.4) and the sleep study procedures (mean 7.8 ± 4.2).

DISCUSSION

In this pilot study of twelve patients with ALS, NIV improved oxygenation, as measured by minimum overnight oxygen saturation and time spent with significant hypo-oxygenation ($\text{SpO}_2 < 90\%$). In this small group of patients, NIV did not have an effect on sleep efficiency, apneas/hypopneas, arousals, or sleep quality/architecture.

Our study is the first study specifically evaluating the effects of NIV on sleep outcomes in ALS. Early NIV has been shown to have positive effects on chronic hypoventilation, quality of life and survival¹²⁻¹⁹ in studies comparing ALS NIV users with patients who refuse or are not able to tolerate NIV. Bourke et al. performed the only randomized, unblinded, controlled trial of NIV in ALS showing that NIV improved quality of life and survival in a group of ALS patients, particularly those with preserved bulbar function.²⁰ Although sleep studies are performed on many of the patients in these studies at the time of NIV initiation, none of the studies systematically evaluated the effects

Table 3—Change in secondary sleep outcomes between NIV and baseline sleep studies

Pts	Age/ Sex	Time to NIV Study (days)	FVC	AI	HI	AHI	Arousal Index	1 st PSG TST (min)	2 nd PSG TST (min)	TST (min)	TSP (min)	Sleep Efficiency (%)	Sleep Latency (min)	Stage 1 Duration (%)	Stage 2 Duration (%)	Stage 3 Duration (%)	REM Duration (%)	Min SpO ₂ (%)
1	85/F	8	39	0	0	0	+3.6	375	206	-169	-165	-11.8	-6	0	0	0	0	-3
2	66/F	13	46	-2.1	+5.7	+3.2	+1.4	432	436	-4	-48	-10.7	-11.5	0	+4.1	0	-6.1	+4
3	89/M	12	70	-22	+21	-1.0	+13	404	169	-235	-193	-24	+4	+6.2	-15.0	0	+8.5	+18
4	27/F	6	62	0	+0.6	+0.6	-13.7	310	540	+230	+188	+12.4	-51.5	-4.5	-14.6	+9.5	+18.7	+7
5	56/M	10	59	+0.5	-20.5	-20	+4.4	421	609	+188	-33	+47.1	-25	-7.3	+9.1	0	-1.8	+6
6	61/M	7	46	0	-4.9	-4.9	-1.8	491	352	-139	-292	+13.1	-14.5	-25.4	+27.3	0	-2.3	-8
7	73/F	7	36	+1.7	-0.3	+1.4	-2.1	535	243	-292	-200	+8	-15.0	0	-7.9	0	+7.9	+22
8	78/M	9	44	0	-2.0	-2.0	+8.1	323	278	-45	+136	-39	+44	+3.0	-7.0	0	+4.0	+19
9	55/M	9	56	+1	+0.2	+1.2	+7	439	453	+14	-23	+6	+23	-10	+10	0	0	+6
10	82/F	7	67	0	+2.0	+2.0	-3.3	333	543	+210	+88	+39	-83	+2	-33	0	+31	+6
11	80/F	12	51	-3.2	0	-3.2	+2.4	415	471	+56	+67	+12	-13.4	-4.5	+6	0	+2.5	+5
12	44/F	8	64	-2.0	-4.5	-6.5	-6.6	485	586	+101	+45	+4	-16	0	-12	+2	+10	+7

Patient age, sex (M = male, F = female), forced vital capacity (FVC) at the time of enrollment into the study prior to the first polysomnogram (PSG) and time from the first sleep study to the second NIV study are reported. Respiratory specific secondary outcome measures included changes in apnea index (AI), hypopnea index (HI), and apnea/hypopnea index (AHI) and other secondary sleep related outcome measures included changes in arousal index, total sleep time (TST), total sleep period (TSP), sleep efficiency, sleep latency, and percentage of time spent in each sleep stage (stages 1-3 and REM). The primary outcome, minimum overnight oxygenation (SpO₂), is presented in the last column for reference.

Table 4—Effects of NIV on secondary outcomes in ALS patients

	Baseline Sleep Study (mean ± SD)	Post-NIV Study (mean ± SD)	Difference*
Apnea index	3.7 ± 7	0.7 ± 1.6	-3
Hypopnea index	6.2 ± 6.8	5.7 ± 7.8	-0.5
Apnea-hypopnea index	9.8 ± 11.1	6.3 ± 8.3	-3.5
Total sleep period (minutes)	525 ± 90	456 ± 153	-69
Total sleep time (minutes)	347 ± 138	346 ± 147	-1
Sleep efficiency (%)	64 ± 21	74 ± 14	+10
Wake after sleep onset (minutes)	145 ± 100	100 ± 59	-45
Arousal index	7 ± 6	12 ± 11	+5
Sleep latency (minutes)	44 ± 38	28 ± 21	-16
Stage 1 duration (%)	7 ± 12	2 ± 2	-5
Stage 2 duration (%)	86 ± 13	85 ± 11	-1
Stage 3 duration (%)	1 ± 2	1 ± 3	0
REM duration (%)	13 ± 23	12 ± 9	-1

SD, standard deviation. *All secondary sleep outcomes were nonsignificant ($p > 0.05$).

of NIV on sleep outcomes. In a precursor pilot study to their randomized study, Bourke et al. performed polysomnography on patients every four months after NIV initiation, however, this data was not reported.²¹ A recent publication evaluated 19 ALS patients recently starting NIV with home sleep studies and found patient-ventilator asynchrony; however, the authors did not perform before-after NIV studies to evaluate the effects of the intervention on sleep outcomes.²²

Our study found a 7% change in minimum overnight oxygen saturation in ALS patients when they used NIV compared to no NIV, which was comparable to our oxygenation target of 5% improvement. This finding suggests that NIV may help to reverse the maximal drop in oxygen saturation in patients with ALS. Very low oxygen saturation levels have been seen in other studies evaluating sleep dysfunction in ALS, and they have been found to occur most prominently during REM com-

pared to other stages of sleep.^{23,24} One explanation for this may be accessory muscle atonia, which occurs during REM sleep when the already weak diaphragm is the only functional respiratory muscle and when NIV can best support breathing and improve oxygenation.^{25,26} We found that half of our patients were not able to achieve REM sleep. In those who were, NIV had greatest effects on oxygenation in this stage of sleep. Another measure of oxygenation which improved with treatment, time spent with saturation < 90%, suggests that the improvements in minimum saturation seen with NIV are clinically significant and not merely brief, transient events. Using only minimum oxygen saturation introduces the possibility of technical error, particularly dislodging of the saturation probe which may occur during the PSG. Other studies evaluating patients with ALS have not found changes in minimum oxygen saturation in response to NIV; but they did find changes of 3% to 5% in mean

overnight saturation when using overnight oximetry.^{27,28} In our cohort, mean oxygen levels also improved, but only by 1.5%, which was not significant.

Although the precise contribution of each type of apnea to sleep disordered breathing in ALS has not been fully characterized, most studies using polysomnography have found central apnea to be the most prominent source of respiratory dysfunction, as was found in our study.²⁹ On occasion, episodes of obstructive apnea may occur in patients with ALS, particularly in patients with bulbar symptoms, where weakness of pharyngeal muscle dilators may cause collapse of the pharyngeal wall and increased upper airway resistance. This was consistent with our study, which found that less than 20% of apneas were obstructive, which is not surprising given that none of our patients were predominantly bulbar or had bulbar onset ALS, and also that patients did not have increased BMI or neck circumference (which are associated with obstructive sleep apnea). It also continues to support the use of bilevel over continuous noninvasive ventilation as is the standard for most patients with neuromuscular disease such as ALS. The low proportion of bulbar onset patients in our treated group likely reflects selection bias mirroring clinical practice in our small group of patients, as patients with severe bulbar disease are less likely to be started on NIV, and skews results towards success as they tend to respond poorly to NIV. Although not significant, bilevel NIV did appear to have a trend toward improving the apnea hypopnea index, which would be consistent with previously reported positive effects in patients with neuromuscular conditions and central apnea.³⁰ Additional study of the effects of NIV on apneas and hypopneas as well as ventilatory outcomes such as end-tidal CO₂ will help to confirm whether improvement in oxygenation is a direct result of the effects respiratory support on nocturnal hypoventilation during these episodes.

Eight of twelve patients in our study had an improvement in sleep efficiency with NIV, with a mean improvement in sleep efficiency of approximately 10%. A number of patients also improved total sleep time on NIV; however, this was decreased overall in the NIV group, which may reflect adjustment to the NIV and also help explain some of the improvement in sleep efficiency from NIV. Sleep efficiency itself declined in four patients, including two patients who showed a reduction in oxygen saturation from normal to subnormal values with treatment. It is unclear why some of these patients worsened with NIV. It is possible that excessively elevated NIV pressure and volume settings may have been at fault, particularly in patients starting with normal baseline overnight oxygen saturation levels, which has been previously described.²³ Indeed, a recent publication has highlighted that patient-ventilator asynchrony occurred frequently in a group of 19 ALS patients studied with PSG.²² In addition, all four of these patients had increased arousal index, which may reflect mask discomfort due to poor fit or mouth dryness. Once patients were asleep, proportion of restful (stage 3 and REM) sleep and overall sleep architecture was not affected by NIV in our cohort. One impressive finding was the lack of stage 3 sleep (1%) found in any of the sleep studies performed with or without NIV, which is much lower than previously reported in other studies, and may be due to the advanced respiratory insufficiency of our patient cohort.^{2,5,24-26}

Our study had various limitations. Our study showed a change in minimum oxygen saturation and time spent with O₂ < 90%; however, interpretation of other markers of sleep dysfunction and subgroup analysis was limited by small patient numbers. We were also limited to studying patients who had an FVC at or below 50%, as this is the stage at which most patients start NIV in the United States due to recommend guidelines⁷ and insurance coverage. This may not be the optimal time to start NIV in all patients, and this issue should be studied further in subsequent studies. Although using home PSG may help to minimize the “first-night effect” compared to hospital based sleep studies, there is inherent variability in the quality, settings, and duration of NIV use between patients, as well as the quality of home, unmonitored sleep studies. An additional night of PSG used to titrate NIV settings prior to the comparison NIV study would also have been helpful to optimize treatment in our cohort. Our study design used patients as their own controls and studying them immediately before and after NIV initiation, which had the benefit of minimizing heterogeneity between treatment and control groups, particularly in respect to the amount of respiratory dysfunction. Lack of a “natural history” comparison group of patients performing two sequential sleep studies who were not using NIV, however, makes it difficult to accurately assess bias that might have been introduced by the PSG itself, particularly inadequate time allowed for maximum compliance and tolerance. Although great care was taken to perform titration more quickly than is the case in the clinical setting to avoid PSG sometimes requires more time for the patient to accommodate fully. Increasing the time between the two studies runs the risk of introducing bias from progression of disease itself, which was the rationale for the four-week gap between NIV studies. Finally, although changes in oxygen saturation were used as the main outcomes in our study, other respiratory markers such as end-tidal carbon dioxide levels and effects on daytime hypercapnia, which are markers of ventilation, may be more clinically meaningful primary outcomes in subsequent larger studies.

Although recent studies have shown that patients with ALS experience difficulty tolerating NIV due to patient-ventilator asynchrony, our study demonstrates that NIV may be beneficial in improving oxygenation even in a small group of ALS patients. Although it is difficult to draw conclusions about subgroups of patients with different levels of respiratory dysfunction or NIV tolerance in our small group of patients, future studies should evaluate these factors in a larger group of patients and establish ways to maximize the effects of NIV in this patient population. In the meantime, NIV remains an important intervention to offer patients with ALS, as has been recommended by the Report of the Quality Standards Subcommittee of the American Academy of Neurology.⁷ The study procedures using home PSG are well tolerated by patients, caregivers, and health care professionals, and may be used as a model to continue to study sleep disordered breathing and sleep dysfunction in ALS.

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